PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07J 13/00, 51/00, 71/00

A1

(11) International Publication Number: **WO 98/18813**

(43) International Publication Date: 7 May 1998 (07.05.98)

(21) International Application Number: PCT/US97/19276

(22) International Filing Date: 22 October 1997 (22.10.97)

(30) Priority Data:
60/029,312 25 October 1996 (25.10.96) US

(71) Applicant *(for all designated States except US)*: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CONROW, Raymond, E. [US/US]; 1008 Colina Vista Lane, Crowley, TX 76036 (US).

(74) Agents: RYAN, Patrick, M. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD OF PREPARING 21-ALKYLATED PREGNA-1,4,16-TRIEN-3,20-DIONES

(57) Abstract

Methods for preparing intermediates for 21-alkylated corticosteroids are discloded. Pregna-1,4,16-trien-3,20-diones are contacted with a base and an alkylating agent to produce corresponding 21-alkylated pregna-1,4,16-trien-3,20-diones.

REFERENCE: AJ
ZALIPSKY et al., USSN: 10/789,489
Atty. Docket No.: ALZ**5015** R1/3222

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

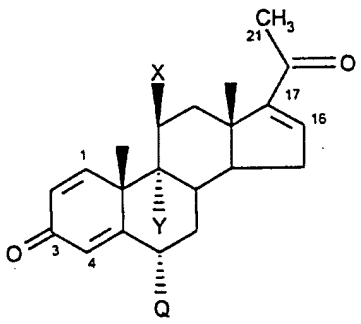
METHOD OF PREPARING 21-ALKYLATED PREGNA-1,4,16-TRIEN-3,20-DIONES

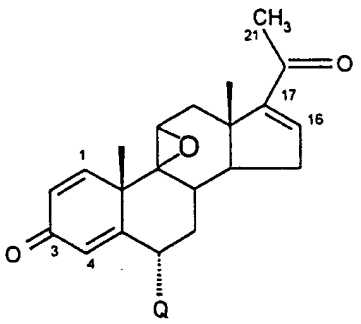
FIELD OF THE INVENTION

The present invention relates to methods of synthesizing intermediates which are used to prepare pharmaceutically active steroids. In particular, the present invention relates to methods of preparing 21-alkylated pregna-1,4,16-trien-3,20-diones.

BACKGROUND OF THE INVENTION

Pregna-1,4,16-trien-3,20-diones of Formula I can be obtained using methods known in the art, for example, methods described in U.S. Patent Nos. 2,874,172; 3,033,873; 3,082,219; 3,281,415; 3,842,105; 4,012,510; and 4,216,159; Vitali et al., Gazz. Chem. Ital., 96:1115 (1966); Hofmeister et al., Chem. Ber., 109: 185 (1976) and Kovendi et al., Rev. Chim. (Bucharest), 27:467 (1976).





wherein X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

R^3, R^4, and R^5 are independently C_1 - C_4 alkyl;

R^6 is H or C_1 - C_4 alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3.

These pregna-1,4,16-trien-3,20-diones are useful for making pharmaceutically valuable corticosteroids.

U.S. Patent Nos. 3,947,478 and 3,862,194 disclose the preparation of pharmaceutically valuable 21-alkylated corticosteroids starting with a 16-pregnen-20-one in which the oxygen functional group at carbon 3 is present in the form of a ketal, enol ether, or protected hydroxyl group. Functional groups are then appended at positions 16 and 17. In a subsequent step, the 21-alkyl group is introduced by, for example, Mannich condensation or ketone alkylation reactions. The 3-keto group is unmasked at a later stage in the synthesis.

Alternative methods of preparing 21-alkylated corticosteroids are desired.

SUMMARY OF THE INVENTION

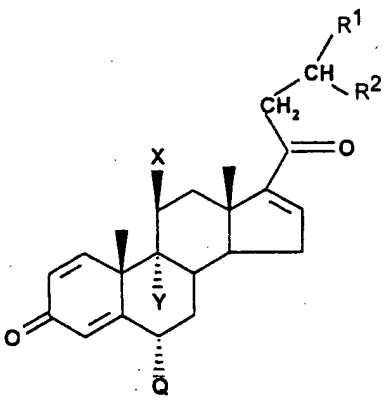
According to the present invention, pregna-1,4,16-trien-3,20-diones are contacted with a base and an alkylating agent in a ketone alkylation reaction to produce corresponding 21-alkylated pregna-1,4,16-trien-3,20-diones. The 21-alkylated products can be converted into pharmaceutically valuable 21-alkylated corticosteroids using techniques known in the art.

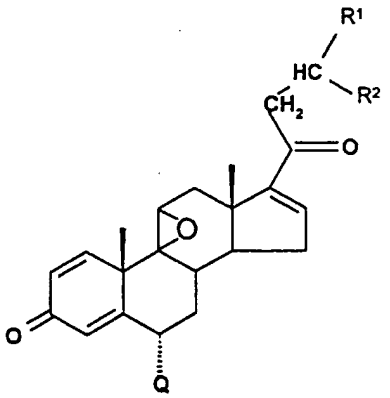
Among other factors, the present invention is based upon the finding that 21-alkylated pregna-1,4,16-trien-3,20-dione intermediates can be readily obtained from pregna-1,4,16-trien-3,20-diones, providing convenient access to pharmaceutically valuable 21-alkylated corticosteroids.

Among other factors, the present invention is also based upon the finding that certain ketone alkylation reactions are highly selective for the 16-en-20-one grouping in the presence of a 1,4-dien-3-one grouping.

DETAILED DESCRIPTION OF THE INVENTION

Ketone alkylation reactions are known in the art. For a discussion of the general chemical methodology employed in such reactions, see d'Angelo, Tetrahedron, 32:2979 (1976). According to the methods of the present invention, ketone alkylation reactions are used to convert pregna-1,4,16-trien-3,20-diones of Formula I above into the corresponding 21-alkylated pregna-1,4,16-trien-3,20-diones of Formula II below.





wherein R^1 and R^2 are independently H or C_1 - C_4 alkyl (optionally unsaturated);

X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

R^3, R^4, and R^5 are independently C_1 - C_4 alkyl;

R^6 is H or C_1 - C_4 alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3.

Preferred compounds of Formula II are those where R^1, R^2, Y, and Q are H; X is $OSiR^3R^4R^5$; and R^3, R^4, and R^5 are CH_3.

According to the present invention, a compound of Formula I is dissolved in a suitable solvent. Suitable solvents generally include, but are not limited to, tetrahydrofuran (THF), glyme, hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), diethyl ether, methyl t-butyl ether, and combinations thereof. Generally, it is desirable to cool the solution to increase the yield of the intended alkylated product. Appropriate temperatures will be determined by those skilled in the art, but will typically range from 0 to -100 °C. In most instances, it is expected that temperatures ranging from -20 to -80 °C will be sufficient for the ketone alkylation reaction to selectively produce the intended product.

Once the solution of the compound of Formula I reaches the chosen temperature, approximately one molar equivalent of base is added. Though other ratios of base to the compound of Formula I could be employed, they are generally not desirable. If an excess of base is used, the chances for side reactions are increased. (An excess of base can form the extended enolate of the A-ring dienone; see Barton et al., J. Chem. Soc., Perkin Trans. I, p. 1075 (1977) and Barton et al., Chem. Comm., p. 1497 (1969)). On the other hand, if less than one equivalent of base is used, the yield is limited. Suitable bases include lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide. The preferred base is lithium hexamethyldisilazide.

After approximately one equivalent of base has been added to the cooled solution of the compound of Formula I, at least one equivalent of an alkylating agent is added. Suitable alkylating agents are those having the formula R^1R^2CHZ, wherein R^1 and R^2 are as defined above; and Z is selected from the group consisting of Br, Cl, and I. Z is preferably Br or I. As one skilled in the art will readily appreciate, it may be necessary or desirable to

allow the reaction temperature to increase after adding the alkylating agent in order to improve the yield.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

Preparation of Pregna-1,4,16-trien-11β-ol-3,20-dione.

a) The method of Kovendi et al., Rev. Chim. (Bucharest), 27:467 (1976) was modified. Semicarbazide hydrochloride (7.1 mL of a 5% aq. solution, 3.2 mmol) was added to a stirred, 50 °C solution of 21-deoxyprednisolone (1.82 g, 5.29 mmol) [see U.S. Patent No. 3,033,873 and Vitali et al., Gazz. Chim. Ital., 96:1115 (1966)] in acetic acid (60 mL) under Ar. The solution was heated to 75-80 °C (internal). After 2.7 h, another 4.7 mL of 5% aq. semicarbazide hydrochloride (2.1 mmol) was added. After 5.5 h at 75 °C, water (50 mL) was added and the solution was heated to 75 °C for 10 h and then to 90 °C for 1.5 h. The solution was cooled to room temperature, poured into 600 mL of water, stirred for 1 h, diluted with water to 1 L, stirred for 0.5 h and filtered on a fritted Buchner funnel. The solid was dried at 80 °C for 3-4 h to a constant weight of 1.00 g (58%, nominal) of crude product, $C_{21}H_{26}O_3$.

Proton NMR ($CDCl_3$): d 1.22 (s, 3H, 18-H_3); 1.48 (s, 3H, 19-H_3), 2.27 (s, 3H, 21-H_3); 1.0-2.7 (m, 12H); 4.38 (br q, 1H, J=2.5, H-11); 6.00 (s, 1H, H-4); 6.25 (dd, 1H, J=10 and 2, H-2); 6.66 (q, 1H, J=2, H-16); 7.32 (d, 1H, J=10, H-1).

This material was converted in 75% yield to the known trimethylsilyl derivative, 11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (Formula I where X = $OSi(CH_3)_3$; Y = Q = H), as described in U.S. Patent No. 4,012, 510.

b) The method of Kovendi et al., Rev. Chim. (Bucharest), 27:467 (1976) was modified. Semicarbazide hydrochloride (4.75 mL of a 5.0 % aq. solution, 2.14 mmol) was added to a stirred solution of 21-deoxyprednisolone (2.15 g, 6.25 mmol) [see U.S. Patent No. 3,033,873 and Vitali et al., Gazz. Chim. Ital., 96:1115 (1966)] in acetic acid (72 mL) under Ar. The solution was heated to 80-85 °C (bath) for 4.2 h. Water (75 mL) was added and heating (85 °C bath) was continued for 5.5 h. The solution was cooled to 23 °C over 11 h, poured into water (850 mL), cooled in ice (to 7 °C) and filtered on a fritted Büchner funnel. The solid was dried under vacuum to give 1.40 g (69%, nominal) of crude product, $C_{21}H_{26}O_3$.

Proton NMR ($CDCl_3$): d 1.22 (s, 3H, 18-H_3); 1.48 (s, 3H, 19-H_3), 2.27 (s, 3H, 21-H_3); 1.0-2.7 (m, 12H); 4.38 (br q, 1H, J=2.5, H-11); 6.00 (s, 1H, H-4); 6.25 (dd, 1H, J=10 and 2, H-2); 6.66 (q, 1H, J=2, H-16); 7.32 (d, 1H, J=10, H-1).

This material was converted in 83% yield to the known trimethylsilyl derivative, 11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (Formula I where X = $OSi(CH_3)_3$; Y = Q = H), as described in U.S. Patent No. 4,012, 510.

EXAMPLE 2

Preparation of 21-Methyl-11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione.

Lithium hexamethyldisilazide (estimated 0.9 M in THF, 2.1 mL, 1.9 mmol) was added over 8 min. to a stirred, cooled (-60 to -65 °C internal) solution of 11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (0.73 g, 1.83 mmol) in THF (12.0 mL) and HMPA (3.0 mL) under Ar. After a further 2 min, the cloudy pale-orange mixture was quenched rapidly with iodomethane (2.5 mL, 40 mmol) whereupon the temperature rose to -57 °C and the suspension cleared. The solution was warmed over 2 min to 10 °C, quenched with sat. KH_2PO_4, and partitioned with EtOAc. The organic solution was dried

($MgSO_4$), filtered and concentrated. The residue (1.9 g) was purified by chromatography (80 g silica, 25% to 50% EtOAc-hexanes) to give 0.62 g (82%) of the product, $C_{25}H_{36}O_3Si$, as an off-white solid, m.p. 178 - 182 °C (dec.).

$[\alpha]^{23}_D$ + 144° (c = 0.05, $CHCl_3$).

IR(KBr) 1660, 1060, 840 cm^{-1}.

Anal. calcd: C, 72.76, H, 8.79. Found: C, 72.57, H, 8.73.

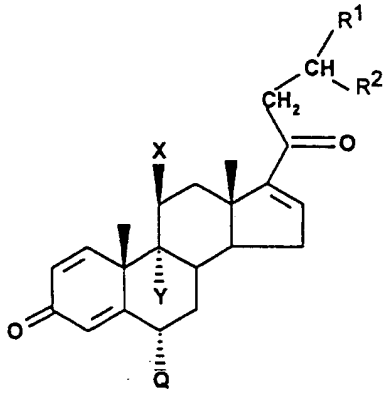
MS (CI, Me_3CH): 413 (m+1)(100), 323 ((m-Me_3SiOH)+1)(10).

Proton NMR ($CDCl_3$): d 0.24 (s, 9H, Me_3Si); 1.05 (t, 3H, J=7.3, Me-21); 1.18 (s, 3H, 18-H_3); 1.41 (s, 3H, 19-H_3); 1.0 - 2.8 (m, 11H); 2.6 (q, 2H, 21-H_2); 4.37 (br q, 1H, J=2.5, H-11); 5.99 (s, 1H, H-4); 6.25 (dd, 1H, J=10 and 2, H-2); 6.64 (q, 1H, J=2, H-16); 7.12 (d, 1H, J=10, H-1).

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A method of preparing a compound of the formula



wherein R^1 and R^2 are independently H or C_1 - C_4 alkyl (optionally unsaturated);

X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

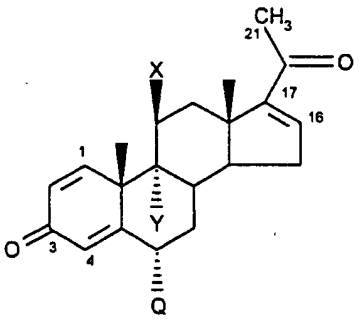
R^3, R^4, and R^5 are independently C_1 - C_4 alkyl;

R^6 is H or C_1 - C_4 alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3;

comprising dissolving a compound of the formula



wherein X, Y, and Q are as defined above,

in a solvent to form a solution and contacting the solution with a base and an alkylating agent.

2. The method of Claim 1 wherein the base is selected from the group consisting of lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide.

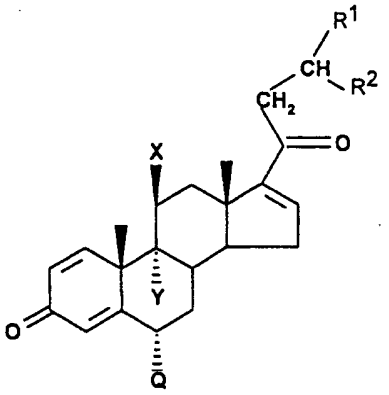
3. The method of Claim 2 wherein the base is lithium hexamethyldisilazide.

4. The method of Claim 1 wherein the alkylating agent has the formula R^1R^2CHZ, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl (optionally unsaturated); and Z is selected from the group consisting of Br, Cl, and I.

5. The method of Claim 4 wherein R^1 and R^2 are H; and Z is selected from the group consisting of Br and I.

6. The method of Claim 1 wherein the solvent is selected from the group consisting of tetrahydrofuran; glyme; hexamethylphosphoramide; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; diethyl ether; methyl t-butyl ether; and combinations thereof.

7. A method of preparing a compound of the formula



wherein R^1 and R^2 are independently H or C_1 - C_4 alkyl (optionally unsaturated);

X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

R^3, R^4, and R^5 are independently C_1 - C_4 alkyl;

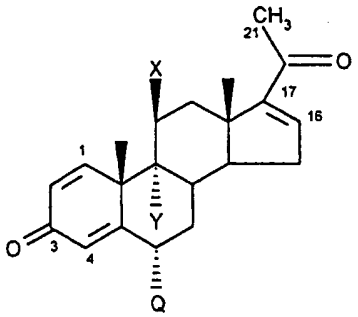
R^6 is H or C_1 - C_4 alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3;

comprising

a) dissolving a compound of the formula



wherein X, Y and Q are as defined above,

in a solvent to obtain a solution;

b) cooling the solution of step (a) to a temperature from about 0 to about -100 °C;

c) adding approximately one equivalent of a base selected from the group consisting of lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide to the cooled solution of step (b); and

d) adding at least one equivalent of an alkylating agent of the formula R^1R^2CHZ, wherein R^1 and R^2 are as defined above; and Z is selected from the group consisting of Br, Cl, and I to the solution of step (c).

8. The method of Claim 7 wherein R^1, R^2, Y, and Q are H; X is $OSiR^3R^4R^5$; and R^3, R^4, and R^5 are CH_3.

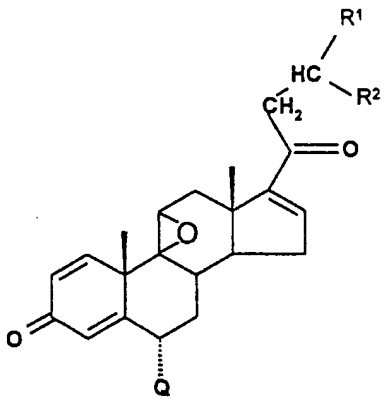
9. The method of Claim 7 wherein the base is lithium hexamethyldisilazide.

10. The method of Claim 7 wherein R^1 and R^2 are H; and Z is selected from the group consisting of Br and I.

11. The method of Claim 7 wherein the solvent is selected from the group consisting of tetrahydrofuran; glyme; hexamethylphosphoramide; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; diethyl ether; methyl t-butyl ether; and combinations thereof.

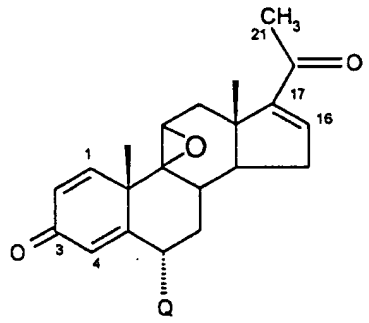
12. The method of Claim 7 wherein the solution of step (a) is cooled to a temperature ranging from about -20 to about -80 °C in step (b).

13. A method of preparing a compound of the formula



wherein R^1 and R^2 are independently H or C_1 - C_4 alkyl (optionally unsaturated); and Q is H or CH_3;

comprising dissolving a compound of the formula



wherein Q is as defined above,

in a solvent to form a solution and contacting the solution with a base and an alkylating agent.

14. The method of Claim 13 wherein the base is selected from the group consisting of lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide.

15. The method of Claim 13 wherein the alkylating agent has the formula R^1R^2CHZ, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl (optionally unsaturated); and Z is selected from the group consisting of Br, Cl, and I.

16. The method of Claim 13 wherein the solvent is selected from the group consisting of tetrahydrofuran; glyme; hexamethylphosphoramide; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; diethyl ether; methyl t-butyl ether; and combinations thereof.

INTERNATIONAL SEARCH REPORT

.ernational Application No
PCT/US 97/19276

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J13/00 C07J51/00 C07J71/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. CAIRNS ET AL: "Alkylated Steroids. Part 3. The 21-Alkylation of 20-Oxopregnanes and Synthesis of a Novel Anti-inflammatory 16.alpha.,17.alpha.,21-Trimethyl Steroid (Org 6216)" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., no. 8, 1981, LETCHWORTH GB, pages 2306-2316, XP002053903	1-16
Y	see page 2311, column 2, last paragraph see page 2306, column 2, paragraph 3 ---	1-16
Y	DE 23 01 317 A (AKZO NV) 26 July 1973 see example 19 ---	1-16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1998	13/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/19276

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. J. WEISS ET AL: "The Formation of Steroid Enolate Anions by Reductive Procedures" TETRAHEDRON., vol. 20, no. 2, February 1964, OXFORD GB, pages 357-372, XP002053904 see page 367, last paragraph	1-16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/19276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2301317 A	26-07-73	GB 1416427 A	03-12-75
		AT 367068 B	25-05-82
		BE 793958 A	12-07-73
		CA 1022158 A	06-12-77
		CH 615934 A	29-02-80
		DK 139031 B	04-12-78
		FR 2168006 A	24-08-73
		JP 1104767 C	16-07-82
		JP 50004060 A	16-01-75
		JP 56014678 B	06-04-81
		NL 7300313 A,B,	16-07-73
		SE 411213 B	10-12-79
		US 3862194 A	21-01-75
		US 3947478 A	30-03-76